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MINIREVIEWS

Considerations and clinical utility of referral pathways for early detection of liver disease in at-risk populations

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Abstract

Metabolic dysfunction-associated steatotic liver disease is the most prevalent chronic liver condition, affecting over one-third of the global population, with cirrhosis present in up to 3.3% of cases. Early detection of advanced liver disease in at-risk populations can enable timely intervention, prevent progression, and reduce complications. This review focuses on the current recommendations for early detection of advanced liver disease, evaluates the evidence for the performance of non-invasive tests in the target population for screening, and examines the multifaceted burden of screening, including economic implications and psychological impacts. Additionally, we discuss future directions, such as integrating liver health into a multidisciplinary care framework. Current guidelines recommend case-finding, targeting individuals with type 2 diabetes, metabolically complicated obesity, or persistent elevated liver enzymes. The Fibrosis-4 index is widely endorsed as a first-line non-invasive test, yet the diagnostic performance in primary care settings seems suboptimal, particularly for pre-cirrhotic disease. Sequential strategies incorporating novel non-invasive tests may improve accuracy and cost-effectiveness. Confirmation typically involves vibration-controlled transient elastography. Key challenges include a large eligible population, uncertainties in optimal screening intervals, patient adherence to follow-up, and limited real-world cost-effectiveness data. Integrating liver health assessment into cardiometabolic care pathways, reflex testing, telehealth, and patient education may enhance uptake. While challenges remain, early detection of advanced liver disease is already likely cost-effective. Ongoing advances in screening pathways and treatment options are expected to further strengthen the case for widespread implementation.

Key Words: Screening; Fibrosis; Advanced liver disease; General population; Epide-

miology

Core Tip: Early detection of liver fibrosis in community settings is essential for timely intervention and to prevent liver related events. Although non-invasive testing strategies are likely cost-effective, their adoption by non-hepatology specialists is limited. Key challenges include the use of overly broad target populations and suboptimal selection or application of non-invasive tests (NITs). Optimizing these pathways by integrating better NITs and refining referral algorithms can improve risk stratification, minimize unnecessary specialist referrals, reduce the burden on healthcare systems, and facilitate timely, multidisciplinary care for individuals at the highest risk for liver-related adverse outcomes.

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INTRODUCTION

Liver disease is becoming increasingly prevalent and poses a significant global problem, with metabolic dysfunction-associated steatotic liver disease (MASLD) being the most common chronic liver disease. Currently, more than 1 in 3 individuals have MASLD, and among them, 3.3% have cirrhosis, which is mostly irreversible[1,2]. In recent years, several guidelines have emphasized the importance of early detection of liver fibrosis to enable timely interventions and prevent progression to advanced liver disease and its complications[3-7]. However, the feasibility of these strategies remains contentious due to the immense strain they place on healthcare systems, the limitations of diagnostic tools, and system level barriers[8-13].

CONSIDERATIONS IN EARLY DETECTION OF LIVER DISEASE: IS SCREENING JUSTIFIED?

Awareness of liver disease is poor among the general population and knowledge is limited among primary care professionals, while the prevalence of MASLD and advanced liver disease is high, raising the question of whether screening is required[1,12,14,15]. The Wilson and Jungner criteria are commonly used to assess whether screening for a disease is justified[16]. These criteria evaluate broad aspects related to the disease itself, the healthcare setting, diagnostic methods, treatment options, and cost-effectiveness (Table 1). Given the typically long asymptomatic phase preceding cirrhosis, a condition associated with high morbidity and mortality, screening for advanced liver disease might prevent symptomatic disease[17-19]. Moreover, with pharmaceutical treatment now available for fibrotic metabolic dysfunction-associated steatohepatitis (MASH) in the United States and lifestyle interventions being potentially effective when adhered to in a pre-cirrhotic stage, early detection may offer a crucial window for intervention and patient education[20,21].

However, several challenges remain: (1) Ensuring adequate facilities for screening and treatment; (2) Determining optimal evaluation and re-evaluation strategies including the choice of non-invasive tests (NITs); and (3) Evaluating and improving cost-effectiveness[22]. Preliminary studies indicate that fibrosis-4 (FIB-4)-based screening strategies may be cost-effective[23-25]. However, real-world data, particularly regarding the long-term impact of such programs, remains limited. With ongoing advances in NITs and the anticipated availability of more effective pharmaceutical agents, the cost-effectiveness of screening is expected to improve. These developments may help overcome the remaining barriers to implementing advanced liver disease screening[26].

While referral pathways can be optimized, the success of screening programs ultimately depends on patient adherence to follow-up testing and specialist care. Concerningly, a German general health screening study found that only 50% of individuals identified as at risk of cirrhosis sought specialist care[27]. This is particularly troubling if screening for advanced liver disease is integrated into a multidisciplinary framework, as in that study, where follow-up attendance was low. Although adherence rates may differ in liver health-specific screening programs as illustrated by vibration controlled transient elastography (VCTE) measurement alongside retina screening (80% attended follow-up visit), monitoring follow-up participation is essential when evaluating referral pathways[28]. Engagement with screening and adherence to follow-up visits might be improved by community-based education, use of telehealth, and artificial intelligence, where possible. The impact of these tools for referral pathway efficacy needs to be proven.

Since the European Association for the Study of the Liver (EASL) NIT guideline in 2021, subsequent guidelines and several position papers have recommended early detection of advanced liver disease in at-risk populations, largely motivated by the anticipated availability of pharmacological therapies and the growing disease burden[3-7,29]. Figure 1 depicts a typical referral pathway. Although not all Wilson and Jungner criteria are fully satisfied, the broad endorsement of early detection of advanced liver disease in at-risk populations underscores the anticipated magnitude of the liver

Table 1 Wilson and Jungner criteria for assessing screening eligibility

Wilson and Jungner criteria	
Disease	The condition sought should be an important health problem
	The natural history of the condition, including development from latent to declared disease, should be adequately understood
	There should be a recognizable latent or early symptomatic stage
Diagnosis	There should be a suitable test or examination
	The test should be acceptable to the population
	Case-finding should be a continuing process and not a "once and for all" project
Treatment	There should be an agreed policy on whom to treat as patients
	There should be an accepted treatment for patients with recognized disease
Setting	Facilities for diagnosis and treatment should be available
Cost-effectiveness	The cost of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole

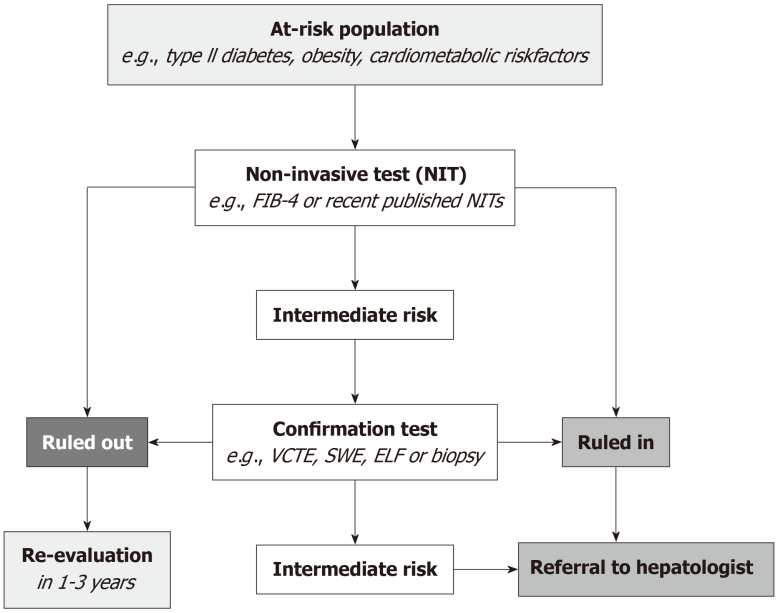

Figure 1 Visual summary of referral strategies recommended by the latest guidelines. NITs: Non-invasive tests; FIB-4: Fibrosis-4; VCTE: Vibration controlled transient elastography; SWE: Shear wave elastography; ELF: Enhanced liver fibrosis.

disease burden.

TARGET POPULATION FOR EARLY DETECTION OF ADVANCED LIVER DISEASE

Screening for advanced liver disease is not feasible in the general population and should instead be targeted to individuals at risk, making it more accurately described as case-finding. Careful initial selection is essential to avoid overburdening already strained healthcare systems and to improve cost-effectiveness by reducing false positives in both primary and validation testing. However, when defining the target population, the yield of the program, particularly its sensitivity, may already be affected[30-32].

The target population for each guideline is summarized in Table 2. Although the guidelines differ slightly, there is general consensus on case-finding for the following subgroups: (1) Type 2 diabetes; (2) Obesity with ≥ 1 other metabolic dysfunction criteria known as metabolically complicated obesity; and (3) Persistent elevated liver enzymes. The metabolic dysfunction criteria in the referral strategies align with the metabolic dysfunction criteria required for MASLD diagnosis and include hypertension, dyslipidemia, and pre-diabetes, among others[33]. Although the European MASLD guideline does not, other guidelines recommend case-finding in individuals with ≥ 2 metabolic dysfunction criteria, even in the absence of abdominal obesity. Similarly, guidelines differ in how elevated liver enzymes are addressed, with varying transaminase cutoff values. The American Association for the Study of Liver Diseases (AASLD) guideline further

Table 2 Summary of guideline recommendations on target population for screening

	Metabolic dysfunction			Elevated ALT	Steatosis
	T2DM	Obesity + ≥ 1 other criteria	≥ 2 criteria		
2021 EASL NIT clinical practice guideline	+	+[1]	+[1]	+[1]	-
2021 AGA clinical care pathway	+	+	+	+	+
2023 AASLD practice guidance	+	+[1]	+[1]	+[2]	+
2024 EASL-EASD-EASO clinical practice guideline	+	+	-	+[3]	+
2025 APASL clinical practice guideline	+	+[4]	+	+	+

[1]Scored yes based on the overarching term "individuals with clinical suspicion of metabolic dysfunction-associated steatotic liver disease such as those with metabolic risk factors" or "at-risk for chronic liver disease (metabolic or alcohol)".
[2]Only an indication when it is unexplained.
[3]Only an indication when it is persistently elevated.
[4]Overweight is also included.
T2DM: Type 2 diabetes mellitus; ALT: Alanine aminotransferase; EASL: European Association for the Study of the Liver; NIT: Non-invasive test; AGA: American Gastroenterological Association; EASD: European Association for the Study of Diabetes; EASO: European Association for the Study of Obesity; APASL: Asian Pacific Association for the Study of Liver; AASLD: American Association for the Study of Liver Diseases.

highlights that first-degree relatives of patients with MASLD cirrhosis, as well as individuals with metabolic dysfunction-associated alcohol-related liver disease, should be considered for case-finding given the particularly high prevalence of advanced fibrosis in these subgroups[6].

Although evidence exists on the prevalence of advanced liver disease for the main criteria, such as type 2 diabetes, metabolic dysfunction, elevated liver enzymes, steatosis (up to 22%), more detailed data on prevalence within the specific subgroups that differ between guidelines remains limited[34,35]. Particularly relevant is the non-obese group with ≥ 2 metabolic dysfunction criteria in the absence of type 2 diabetes. Further evidence is needed to determine the size of this subgroup and to assess whether they require screening or can be safely excluded, thereby improving the feasibility of screening programs.

Application of the AASLD or American Gastroenterological Association selection criteria makes 70% of the United States adult population eligible for screening due to the high prevalence of metabolic dysfunction in this population[10,11]. Although this number might be substantially lower in countries with lower obesity rates, it is important to investigate whether the target population can be safely refined. Recent data underscore the importance of alcohol consumption (even within normal range) on disease progression and potential interactions with metabolic dysfunction[36-38]. Similarly, systemic inflammation is crucial in the progression from MASLD to more advanced disease (*e.g.*, MASH and eventually fibrosis) and might, therefore, have predictive value[39]. However, adding further complexity to the screening algorithm may reduce its clinical utility and should be avoided when incorporating alcohol use or inflammation provides only marginal benefit.

Current guidelines do not suggest appropriate age ranges for screening. The clinical benefit and utility of liver fibrosis screening algorithms in patients aged over 65 should ultimately be evaluated through cost-effectiveness studies[40]. These studies have not yet been conducted in community-dwelling older adults, in whom neither steatosis nor liver stiffness measurement (LSM) ≥ 8 kPa is associated with all-cause mortality, unlike in younger and middle-aged populations[41-46]. Although these findings require further validation, this would advocate against screening for liver disease in older adult populations. The absence of increased mortality in older adults with steatosis or LSM ≥ 8 kPa may be explained by healthy survivor bias, as well as the presence of cardiovascular risk management programs targeting this subgroup. This aims at reducing cardiovascular mortality, the primary cause of death in MASLD patients[47]. Other screening programs, such as those for colorectal cancer or breast cancer, typically stop at age 75, which may be considered the upper age limit for liver disease screening[48,49]. Additionally, treatment availability is a prerequisite for the feasibility of screening[16]. Although Resmetirom was investigated among individuals aged ≥ 18 years, no subgroup analysis by age was performed. Assuming a normal distribution, only 11% (36-37 individuals per treatment arm) of this study population was aged > 70 years[20]. Therefore, potential screening and treatment initiation above this age should be performed with caution, and additional evidence is required. Therefore, we recommend that screening programs focus on young to middle-aged populations, while evidence on treatment efficacy in other age groups for long-term outcomes is still awaited.

PRIMARY NIT FOR RULING OUT ADVANCED LIVER DISEASE IN AT-RISK POPULATIONS

Although a chronically elevated alanine aminotransferase (ALT) level is an important indicator for screening, it has insufficient discriminative accuracy to rule out clinically significant liver disease[50]. To address this critical clinical need, various NITs have been developed, are readily available [*e.g.*, FIB-4, nonalcoholic fatty liver disease fibrosis score (NFS) and LSM] and have demonstrated a similar prognostic value for future liver-related events compared to histologically assessed fibrosis grades[51]. This supports the use of NITs, particularly in a screening or case-finding setting where more invasive approaches, such as liver biopsy, are not feasible.

The FIB-4 is the cornerstone of currently recommended referral pathways and consists of readily available parameters: Aspartate aminotransferase, ALT, platelets, and age. The FIB-4 is inexpensive and well-known and, therefore, has been selected as the first-line test[3-7]. The recommended cut-offs are consistent across guidelines: 1.3 to rule out disease and 2.67 for direct referral to a hepatologist, while values between 1.3 and 2.67 require a confirmation test, which may also be performed by other healthcare providers (Table 3)[3-7].

However, incorporating age as a parameter in NITs, such as the FIB-4, raises important performance issues, as highlighted by several studies[8,52-59]. Although including age as a linear covariate generally improves accuracy, it compromises performance in both younger and older populations. To overcome this issue, an age-dependent cut-off of 2.0 instead of 1.3 has been proposed and applied by most guidelines. Although this cut-off helps reduce the number of false positives in older adult populations, it decreases sensitivity by one-third and is therefore debated[56]. Furthermore, although this suboptimal solution can be used for older adults, it does not resolve the poor sensitivity in individuals < 35 years. Therefore, alternatives need to be considered[6].

Despite being inexpensive and easy to perform, the widespread adoption of FIB-4 in referral pathways was not evidence-based when implemented. Originally developed to identify ≥ F3 fibrosis in patients co-infected with human immunodeficiency virus and hepatitis C, its diagnostic accuracy for detecting elevated LSM in the target population of these screening algorithms appears limited, as consistently reported in multiple studies following the inclusion of FIB-4 in the guidelines[8-11,60]. The poor performance of FIB-4 in the target screening population contrasts with its results in MASLD patients currently under hepatologist care and undergoing liver biopsy in secondary or tertiary hospital settings [61]. However, it should be noted that this is a highly selected population that was already identified for referral on other grounds, and therefore does not reflect the overall MASLD population. This is illustrated by the fact that these patients exhibit advanced liver fibrosis in 20% of cases, which is far more prevalent than in the population-based setting where approximately 5% is expected. Importantly, NIT performance depends on the *a priori* chance of advanced liver disease, which thus strongly depends on the line of care for which it is used (*i.e.*, primary care *vs* secondary or tertiary care).

Several promising NITs have recently become available that aid in risk stratification and appear to outperform currently available NITs (Table 4)[62-69]. These new scores typically incorporate parameters of metabolic dysfunction, a key driver of fibrosis progression. A step-wise approach, in which a series of NITs is applied sequentially, may ultimately be more cost-effective and provide higher accuracy than using a single NIT followed by confirmation with LSM or enhanced liver fibrosis (ELF). However, evidence from a screening setting is still needed[56,70,71].

Head-to-head comparison of NITs based on sensitivity, specificity, and predictive values are challenging due to differences in their diagnostic purposes and derivation from different populations (Table 4). However, in a study directly comparing the diagnostic accuracy of ten NITs as first-line tests in a general population with metabolic dysfunction, the metabolic dysfunction-associated fibrosis 5 (MAF-5) score performed best for predicting LSM ≥ 8 kPa, LSM ≥ 12 kPa, at-risk MASH and advanced fibrosis. The steatosis-associated fibrosis estimator score was the most accurate for identifying cirrhosis. In contrast, FIB-4, the guideline-recommended first-line test, showed poor performance for pre-cirrhotic disease but was effective for cirrhosis[72]. For example, to achieve 80% sensitivity for LSM ≥ 8 kPa, MAF-5 required fewer referrals (42%) than FIB-4 (77%), with higher specificity (62% *vs* 24%) and positive predictive values of 6-15%. Additional details, including results for other tests, are provided in Table 5.

CONFIRMATORY NIT FOR DIAGNOSING ADVANCED LIVER DISEASE WHEN THE PRIMARY SCREENING TEST IS INCONCLUSIVE

Although liver biopsy remains the gold standard for diagnosing and staging fibrosis, it is not suitable as an initial confirmatory test due to its invasive nature and the relatively low prevalence of advanced liver disease following primary screening[10,11]. VCTE plays an important role in confirmation, with LSM < 8 kPa serving as a threshold to rule out advanced liver disease across all guidelines, requiring no further specialist evaluation (Table 6). Conversely, LSM ≥ 8 kPa warrants specialist follow-up, and repeat VCTE within 3 years may be considered for values ≤ 12 kPa, thereby reducing workload (Table 5)[3-7]. This approach is particularly noteworthy, as approximately 40% of individuals with an LSM ≥ 8 kPa had LSM < 8 kPa upon retesting without any intervention.

Alternative confirmation tests when VCTE is not available vary across the guidelines but include ELF, FibroMeter, Fibrotest, shear wave elastography and magnetic resonance elastography (MRE). ELF has been adopted in the United Kingdom as a primary confirmation test.

MRE offers a highly accurate diagnosis of advanced liver fibrosis[73]. A major advantage is its reduced susceptibility to sampling bias compared to liver biopsy or VCTE, as it evaluates the entire liver volume rather than a small sample. This minimizes the risk of missing fibrosis in a heterogeneously affected liver, where localized sampling may fail to detect disease. However, MRE's high cost, limited availability and long scan times restrict its widespread use in clinical practice. Similarly, ELF, which is based upon three serum biomarkers (hyaluronic acid, procollagen III, tissue inhibitor of metallo-

Table 3 Recommended primary non-invasive tests for screening for liver disease in at-risk populations

	Rule out	Rule in
2021 EASL NIT clinical practice guideline	FIB-4: < 1.3	FIB-4: ≥ 2.67
2021 AGA clinical care pathway	FIB-4: < 1.3 (2.0 aged ≥ 65 years)	FIB-4: ≥ 2.67
2023 AASLD practice guidance	FIB-4: < 1.3 (< 2.0 aged ≥ 65 years)	FIB-4: ≥ 2.67
2024 EASL-EASD-EASO clinical practice guideline	FIB-4: < 1.3 (2.0 aged ≥ 65 years)	FIB-4: ≥ 2.67
2025 APASL clinical practice guideline	FIB-4: 1.3 NFS[1]	FIB-4: ≥ 2.67 NFS[1]

[1]No cut-offs have been provided in the guideline.
FIB-4: Fibrosis-4; NFS: Nonalcoholic fatty liver disease fibrosis score; EASL: European Association for the Study of the Liver; NIT: Non-invasive test; AGA: American Gastroenterological Association; EASD: European Association for the Study of Diabetes; EASO: European Association for the Study of Obesity; APASL: Asian Pacific Association for the Study of Liver; AASLD: American Association for the Study of Liver Diseases.

Table 4 Recently presented non-invasive tests for liver disease detection

	Components	Target	Derivation population
SAFE	Age, BMI, diabetes, AST, ALT, globulin, platelets	≥ F2 fibrosis	MASLD patients
LRS	Age, sex, fasting glucose, cholesterol, AST, ALT, GGT and platelets	LSM (score correlates with expected LSM)	General population/primary care population
MAF-5	BMI, waist circumference, diabetes AST and platelets	≥ LSM 8 kPa	General population
FIB-9	AST, ALT, GGT, ALP, bilirubin, albumin, platelets, prothrombin index and urea	≥ F2 fibrosis	MASLD patients
LiverPRO	Age, AST, GGT, alkaline phosphatase, total cholesterol, sodium, INR, bilirubin, albumin, platelets	≥ F2 fibrosis	At-risk metALD population
acMASH	AST, creatine	MASH	MASLD patients
CORE	Age, sex, GGT, AST, ALT	Liver related events	General population
CLivD	Age, sex, alcohol use, waist-hip ratio, diabetes, smoking, with or without GGT values	Fatal and non-fatal advanced liver disease	General population

SAFE: Steatosis-associated fibrosis estimator; LRS: Liver risk score; MAF-5: Metabolic dysfunction-associated fibrosis 5; FIB-9: Fibrosis-9; acMASH: Aspartate aminotransferase creatinine metabolic dysfunction-associated steatohepatitis index; CORE: A new risk score measuring gamma-glutamyl transferase, aspartate aminotransferase, and alanine aminotransferase; ClivD: Chronic liver disease; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; INR: International normalized ratio; LSM: Liver stiffness measurement; MASH: Metabolic dysfunction-associated steatohepatitis; MASLD: Metabolic dysfunction-associated steatotic liver disease; metALD: Metabolic and alcohol-associated liver disease.

proteinases-1), demonstrates good diagnostic performance for advanced fibrosis[74]. However, its limited availability outside the United Kingdom due to its reliance on highly specialized laboratory measurements hinders routine adoption. It should be noted that the correlation between imaging-based and laboratory-based tests is generally weak to moderate, and confirmation using ELF score or VCTE may select different patient populations[75,76]. Therefore, widespread implementation in screening programs requires careful evaluation, and comparisons of efficacy with VCTE-based referral pathways are warranted.

RE-EVALUATION STRATEGIES IN THE ABSENCE OF SIGNIFICANT LIVER DISEASE

Once screened, at-risk individuals should undergo periodic reassessment with additional testing, which is a key requirement for effective screening programs[16]. The guidelines recommend reassessment between 1 and 3 years of initial assessment (Table 7). The AASLD guideline is more specific and recommends 1-2 years in individuals with type 2 diabetes mellitus (T2DM) or ≥ 2 metabolic risk factors and 2-3 years if these conditions are not present. However, almost the entire target population meets the AASLD criteria for early re-evaluation, as only those who opted for screening due to presence of steatosis or elevated ALT (in the absence of metabolic dysfunction) can be considered for re-evaluation in 2-3 years. Considering the natural disease history, where it typically takes 7 years to progress to the next stage of disease,

Table 5 Test characteristics to obtain 80% sensitivity in a general population setting

	Cut-off	Specificity (%)	NPV	PPV
FIB-4	0.73	24	0.93	0.08
SAFE	-7.04	52	0.97	0.12
LRS	4.98	46	0.97	0.11
MAF-5	-0.37	62	0.97	0.15
CORE	0.0018	37	0.96	0.10

FIB-4: Fibrosis-4; SAFE: Steatosis-associated fibrosis estimator; LRS: Liver risk score; MAF-5: Metabolic dysfunction-associated fibrosis 5; CORE: A new risk score measuring gamma-glutamyl transferase, aspartate aminotransferase, and alanine aminotransferase; NPV: Negative predictive value; PPV: Positive predictive value. Data was extracted from Van Kleef *et al*[72]. Citation: Van Kleef LA, Pustjens J, Schattenberg JM, Holleboom AG, Castro Cabezas M, Tushuizen ME, de Knegt RJ, Ikram MA, Janssen HLA, Francque SM, Brouwer WP. Comparison of diagnostic accuracy and utility of non-invasive tests for clinically significant liver disease in a general population with metabolic dysfunction. *Hepatology* 2025.

Table 6 Confirmatory non-invasive tests to diagnose advanced liver disease when the primary non-invasive test is inconclusive

	Rule out	Rule in
2021 EASL NIT clinical practice guideline	LSM: < 8 kPa	LSM: ≥ 8 kPa
	Alternatives: ELF, FibroMeter, Fibrotest	Alternatives: ELF, FibroMeter, Fibrotest
2021 AGA clinical care pathway	LSM: < 8 kPa	LSM: ≥ 12 kPa
	Alternatives: SWE, ultrasound	Alternatives: SWE, ultrasound
2023 AASLD practice guidance	LSM: < 8 kPa	LSM: ≥ 8 kPa
		Alternatives: ELF
2024 EASL-EASD-EASO clinical practice guideline	LSM: < 8 kPa	LSM: ≥ 8 kPa
		Alternatives: MRE, SWE or ELF with adjusted thresholds
2025 APASL clinical practice guideline	Not mentioned	LSM: ≥ 12 kPa, SWE ≥ 8 kPa, MRE ≥ 3.6 kPa, ELF ≥ 9.8, ADAPT ≥ 6.328

EASL: European Association for the Study of the Liver; NIT: Non-invasive test; AGA: American Gastroenterological Association; EASD: European Association for the Study of Diabetes; EASO: European Association for the Study of Obesity; APASL: Asian Pacific Association for the Study of Liver; AASLD: American Association for the Study of Liver Diseases; ELF: Enhanced liver fibrosis; SWE: Shear wave elastography; MRE: Magnetic resonance elastography; ADAPT: Age, diabetes, N-terminal propeptide of type III collagen and platelets panel; LSM: Liver stiffness measurement.

this screening interval might be too conservative. However, up to 20% of patients are fast progressors, where these shorter intervals are warranted[77,78]. Additionally, due to false negative results with the initial screening test, one may opt for a second test earlier than the average time required for disease progression to maintain trust in screening programs[79]. Although recommendations are provided by the guidelines, data on which intervals are safe in a screening setting are currently lacking and may differ based on the indication for screening and previous test results. Current ongoing projects, such as LiverScreen and LiverAIM, will further investigate what intervals are safe for re-evaluation in a screening setting[22].

Previous studies indicated the value of repeated testing. For example, studies of dynamic changes in FIB-4 have shown that individuals initially classified as intermediate risk who transitioned to the low-risk group within 5 years were not at increased risk of liver-related events. Nonetheless, almost 50% of all liver-related events occurred in the 67% of the general Swedish population that had low FIB-4 on two occasions[80]. This is inferior to the results for MAF-5 from the United Kingdom biobank. There, just 25% of the incident cirrhosis, liver cancer and liver-related mortality occurred in the 70% of individuals with MAF-5 < 1 (low-risk and indeterminate risk). Moreover, like FIB-4, dynamic changes were associated with risk changes overtime[81]. However, another study reported only weak associations with changes in FIB-4, aspartate aminotransferase to platelet ratio index and NFS with disease progression in MASLD patients[82].

Re-evaluation for liver disease may eventually be a dynamic process similar to the colon cancer screening test where risk factors are considered together with findings during colonoscopy in case of a positive screening test[83,84]. If there is a subgroup where extended screening intervals for significant liver disease appear to be safe, this would increase screening program feasibility.

Table 7 Recommended re-evaluation strategies

	Interval	Early re-evaluation	Screening test
2021 EASL NIT clinical practice guideline	1-3 years		FIB-4
2021 AGA clinical care pathway	2-3 years		FIB-4
2023 AASLD practice guidance	2-3 years	After 1-2 years in individuals with T2DM or ≥ 2 metabolic risk factors	FIB-4
2024 EASL-EASD-EASO clinical practice guideline	1-3 years	Within 1 year when FIB-4 was indeterminate and management of comorbidities was intensified, whilst VCTE was not performed	FIB-4
2025 APASL clinical practice guideline	2-3 years		FIB-4, NFS

EASL: European Association for the Study of the Liver; NIT: Non-invasive test; AGA: American Gastroenterological Association; EASD: European Association for the Study of Diabetes; EASO: European Association for the Study of Obesity; APASL: Asian Pacific Association for the Study of Liver; AASLD: American Association for the Study of Liver Diseases; VCTE: Vibration controlled transient elastography; FIB-4: Fibrosis-4; T2DM: Type 2 diabetes mellitus; NFS: Nonalcoholic fatty liver disease fibrosis score.

EVIDENCE OF NIT PERFORMANCE IN THE GENERAL POPULATION

Several challenges in NIT development can affect performance in screening programs. Key decisions include defining the target outcome, such as increased LSM, histology-based advanced fibrosis, or liver-related events including hepatocellular carcinoma and decompensated cirrhosis, and the population in which the model is trained (*e.g.*, general *vs* hospital-based population). Ideally, the development setting should match the intended screening setting; for example, an NIT intended for population screening would ideally be developed in a general population with available liver biopsy data. Because this ideal scenario is not feasible, compromises must be made, which can affect the utility of the score in screening programs and should be considered during implementation. Most NITs have been developed in hospital-based populations, as biopsy data are generally unavailable in the general population. However, these populations represent only the "tip of the iceberg", with more advanced liver disease, limiting the generalizability of these NITs to the broader screening population. On the other hand, the MAF-5 and liver risk score were developed in a more general population setting and were trained on increased liver stiffness due to lack of biopsy[63,64]. Interestingly, CORE, a new risk score measuring gamma-glutamyl transferase, aspartate aminotransferase, and ALT, used a Swedish registry and did not consider fibrosis, but major adverse liver-related outcomes, events that need to be prevented by screening programs[68]. Due to differences in populations where NITs are developed and are employed, differences might occur between performance in the development populations and the actual performance in a screening setting. Therefore, the study population in which the NIT is developed should be considered when deployed in referral strategies and is preferably similar to the target screening population.

COST-EFFECTIVENESS AND BURDEN OF SCREENING

Screening programs for advanced liver disease initially increase costs but become cost-effective, not necessarily cost-saving, long-term by the expected reduced mortality and advanced fibrosis rates, thereby lowering long-term expenses [85]. Several studies have used Markov models to evaluate the long-term costs and cost *per* quality-adjusted life year (QALY) of various screening strategies[23,24,86,87]. In a study on participants with type 2 diabetes, all investigated NITs were associated with improved QALYs, with the most substantial gains from VCTE, followed by FIB-4, ELF, and NFS[23]. Similarly, a Korean study assessing a sequential approach of FIB-4 followed by VCTE in at-risk populations (T2DM, obesity, metabolic syndrome), reported incremental cost of 298 dollars and a 0.0199 QALY gain *per* patient. This corresponds to a cost of 14949 dollars *per* QALY gained, which is well below the national willingness-to-pay threshold of 25000 dollars *per* QALY in Korea, indicating cost-effectiveness. When the broader benefits of treatment, such as reductions in cardiovascular and cancer-related morbidity were incorporated, cost-effectiveness further improved, with an incremental cost-effectiveness ratio of 12749 dollars *per* QALY. These findings indicate that if liver fibrosis screening with currently available NITs were implemented in primary care, it would likely be cost effective. Notably, upcoming pharmacological treatments may contribute even more to cost-effectiveness compared to the current standard of care, particularly because lifestyle interventions are notoriously difficult for patients to adhere to[88,89].

Besides economical costs, the social and psychological burden of liver disease screening should not be underestimated, particularly given the high false positive rate associated with current NITs. At present, no available test yields more true positives than false positives. Insights from breast cancer screening programs have shown that false positive results can have lasting psychosocial consequences and reduce willingness to participate in future screening rounds[90,91]. While data on the psychological impact of liver disease screening are limited, studies indicate that more than half of individuals newly diagnosed with MASLD report symptoms of anxiety[92]. This may be in part linked to stigmas surrounding liver

disease. Many individuals with chronic liver disease express fear of being labeled as alcoholics[93]. Therefore, the potential for false positive results must be clearly communicated to patients and, ideally minimized through optimized screening strategies[94].

LIVER FIBROSIS SCREENING AS PART OF A MULTIDISCIPLINARY APPROACH

Although MASLD is an important risk factor for liver-related complications and mortality, only a subset of individuals will progress to advanced liver disease[17,19]. Among MASLD patients, cardiovascular disease is the primary cause of death, which illustrates that MASLD management cannot be separated from cardiovascular risk management, and a more holistic management approach is warranted[18].

The updated 2025 American Diabetes Association guideline now includes a section on mitigating the risk of MASLD and MASH, recommending assessment of liver health and consideration of incretin-based therapies, which may offer benefits in these conditions[95]. Moreover, the new obesity definition now includes MASLD with fibrosis as one of the comorbidities requiring investigation[96]. Similarly, a Delphi consensus paper on the management of MASLD in cardiovascular disease agreed on screening for MASLD and fibrosis in type 2 diabetes, metabolic syndrome, overweight/obesity and argued for a screening pathway of MASLD and fibrosis in cardiovascular disease management using imaging and or NITs. Moreover, they also urged screening for cardiovascular disease in MASLD patients[18]. Altogether, there is momentum in increasing awareness of liver health by health care providers, particularly among those who treat metabolic dysfunction.

In the future, liver disease screening may even be integrated into cardiovascular risk management. For example, NIT-based screening could be implemented as reflex tests in those with cardiometabolic disorders. A recent study proposed an innovative approach in which VCTE measurement was performed following diabetic retinopathy screening, resulting in a high participation rate for fibrosis screening[28]. However, this approach deals with a selected population that was already engaged in a screening program. Another study implemented automatic fibrosis score (FIB-4 and aspartate aminotransferase to platelet ratio index) calculations and electronic reminder messages in a randomized controlled setting for those with type II diabetes attending medical or diabetes clinics[97]. Implementation of this care pathway increased appropriate referral for hepatology assessment or further fibrosis tests in patients with increased fibrosis scores from 3.1% to 33.3%. These results suggest that incorporating NIT-based reflex testing could enhance early liver fibrosis detection. Unfortunately, implementation of these clinical care pathways remains in its early stages, although important steps have been made.

CONCLUSION

Early detection of advanced liver disease in at-risk individuals is important both for patient education and for preventing future liver-related events, and it is likely already cost-effective in its current form. Although referral strategies have been successfully developed, they are not yet widely adopted by non-hepatology healthcare providers. Remaining challenges include overly broad target populations, suboptimal selection of the initial NIT from a screening perspective, and limited data on safe screening intervals. These obstacles may be addressed through early reassessment of existing referral pathways and the integration of recently developed NITs.

FOOTNOTES

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